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13. ABSTRACT *(Maximum 200 Words)*

The purpose of this research is to investigate whether eating brown seaweed (*Undaria pinnatifida*) and soy powder can influence hormone levels that are thought to affect breast cancer risk. Brown seaweeds and soy foods are popular in Japan, where the incidence of breast cancer is about 1/6 the rate of that reported for American women. In several animal studies of diet and cancer, adding seaweed or soy to the normal diet resulted in longer healthy lives. Many studies have found that soy consumption in Asia appears to be linked directly to lower breast cancer risk, and laboratory studies have confirmed that soy reduces tumors in animal models. Constituents of soy have been proposed as antiestrogens and antioxidants, may induce apoptosis, and inhibit topoisomerase and angiogenesis (Zheng, 1999). We want to investigate how eating seaweed and soy together might affect hormone levels predictive of women's health. We will use commercially available seaweed and soy powder. These seaweeds and soy powder are commonly found in health food stores.

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Introduction

Breast cancer rates are significantly lower among women in Asia, particularly postmenopausally. Women who move to the US increase their risk to US rates within two generations, suggesting that lifestyle factors, rather than genetic differences, are responsible. Dietary preferences, because they can pervasively alter an individual's exposure to daily carcinogens and anticarcinogens, are thought to be important in explaining international differences in breast cancer rates.

Two foods, seaweeds and soy products, are commonly eaten in Asia, but rarely eaten in the US. In several international studies, soy intake has been found to be associated with lower breast cancer risk. Many studies have found that soy consumption in Asia appears to be linked directly to lower breast cancer risk, and laboratory studies have confirmed that soy reduces tumors in animal models. Constituents of soy have been proposed as antiestrogens and antioxidants. In addition, studies of soy constituents have been shown to induce apoptosis, and inhibit topoisomerase and angiogenesis (Kurzer, 1997). Two review papers by the Principal Investigator have hypothesized that consuming seaweed would be protective against developing breast cancer (Teas, 1983; Teas, 1981).

Brown seaweeds and soy foods are popular in Japan, where the incidence of breast cancer is about 1/6 the rate of that reported for American women. In several animal studies of diet and cancer, adding seaweed or soy to the normal diet resulted in longer healthy lives. In several international studies, soy intake has been found associated with lower breast cancer risk. Many studies have found that soy consumption in Asia appears to be linked directly to lower breast cancer risk, and laboratory studies have confirmed that soy reduces tumors in animal models. Constituents of soy have been proposed as antiestrogens and antioxidants, may induce apoptosis, and inhibit topoisomerase and angiogenesis (Zheng, 1999). We want to investigate how eating seaweed and soy together might affect hormone levels predictive of women's health. Phytoestrogens have been found to protective against osteoporosis and cardiovascular disease (Wiseman, 2000; Glazier, 2001). We will use commercially available seaweed and special calcium-reduced soy powder produced by Protein Technologies International. This seaweed and a similar soy powder are commonly found in health food stores.

Seaweed, on the other hand, has received only minimal scientific scrutiny. This may be due to the small amount eaten, 5 to 7 g/d, in a normal diet even in Japan, where seaweed is eaten more commonly (Toyokawa, 1979). It may also reflect a cultural prejudice against eating seaweeds in the US and Europe.

Several studies have found that seaweed extracts are effective against tumors in animals and inhibit tumor cell growth in culture. In addition, our early work demonstrated that dietary seaweed protected rats from developing dimethyl benzanthracene (DMBA) - induced mammary tumors (Teas, 1984). Similar findings from a more recent study by Funahashi indicate that *Undaria* also suppresses DMBA-induced mammary tumors (Funahashi, 1999).

Body

The purpose of this research is to investigate whether eating brown seaweed (*Undaria pinnatifida*) and soy powder can influence hormone levels that are thought to affect breast cancer risk. We will focus on three primary surrogate endpoint biomarkers of breast cancer: estrogen metabolism (phytoestrogen excretion and the 2 hydroxyestrone: 16 alpha- hydroxyestrone), urinary excretion of melatonin, and changes in plasma lipids. We will also monitor changes in thyroid hormones to assess any possible negative effects of seaweed supplementation, and urinary excretion of iodine as a marker of adherence to seaweed supplementation.

We hope to prove/disprove that consuming 5 grams of seaweed with and without high isoflavone soy supplement will modify surrogate biomarkers of breast cancer risk. Several possible mechanisms are postulated as candidates for modulation by these dietary supplements. These include:estrogen metabolism (2 hydroxyestrone/16 alpha-hydroxyestrone ratio (2 OHE_1/16 α OHE_1), melatonin, phytoestrogen metabolism, plasma lipids, and thyroid hormones. A blinded, crossover study design will serve to address the issues of any carry-over effect of seaweed after cessation of seaweed intake.

Specific Aims:

Aim 1 We propose that seaweed and seaweed plus soy will increase the ratio of urinary estrogen metabolites 2 OHE_1/16 α OHE_1 (2/16).

Aim 2 Our hypothesis is that consuming 5 g/d of Undaria seaweed will increase urinary excretion of 6-sulfatoxymelatonin.

Aim 3 We propose that soy alone and seaweed plus soy will enhance isoflavone and lignan derived phytoestrogen excretion. The combination of soy and seaweed may act either additively or synergistically.

Aim 4 We propose that both seaweed and soy will decrease cholesterol levels and triglycerides, and that this decrease will be either additive or synergistic.

Aim 5 We propose that thyroid hormones will be altered by seaweed consumption. In our previous study we used *Alaria esculenta*, a brown seaweed with approximately 100 ug/g of iodine. In this study, we will use *Undaria pinnatifida* which has only about half as much iodine. We are also interested in how the low iodine-containing *Undaria* will affect thyroid hormones.

Progress to date

The progress since last year has consisted entirely in addressing the concerns of the Human Protection Specialists. I worked with Ms. Jarsie Weeks until she left the Agency, the very week my final revisions were submitted. Then I have worked with Dr. Mary

Ann Pranulis since then. My study was reviewed by HSRRB on March 27, 2002. Because of various concerns, a decision on my study was postponed until I submitted additional information. I have done so, and am currently awaiting a new date for HSRRB review. No work on this grant can be initiated until final approval from HSRRB is granted.

KEY RESEARCH ACCOMPLISHMENTS

I have satisfied the research and human protection concerns of two different Human Protection Specialists.

I have attended the HSRRB review of my study, and have responded to their concerns.

REPORTABLE OUTCOMES:

None.

CONCLUSIONS:

Obtaining HSRRB approval for my low risk, minimally invasive (dietary supplementation, blood samples, and urine collection) is very difficult.

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